

23 2002

DEMARK OFFICE 6601

LAHIVE  
&  
COCKFIELD  
L L P

COUNSELLORS AT LAW  
28 STATE STREET  
BOSTON, MASSACHUSETTS 02109-1784  
TELEPHONE (617) 227-7400  
FAX (617) 742-4214  
lc@lahive.com

JOHN A. LAHIVE, JR. (1928-1997)  
THOMAS V. SMURZYNSKI  
RALPH A. LOREN  
GIULIO A. DeCONTI, JR.  
ANN LAMPORT HAMMITTE  
ELIZABETH A. HANLEY  
AMY BAKER MANDRAGOURAS  
ANTHONY A. LAURENTANO  
KEVIN J. CANNING  
JANE E. REMILLARD  
DeANN FORAN SMITH  
PETER C. LAURO  
JEANNE M. DIGIORGIO  
DEBRA J. MILASINIC, Ph.D.  
DAVID J. RIKKERS  
DAVID R. BURNS  
JOHN S. CURRAN  
SEAN D. DETWEILER

CYNTHIA L. KANIK, Ph.D.  
MEGAN E. WILLIAMS, Ph.D.  
RICHANAND  
MICHAEL PHILLIPPS \*  
LISA M. DIROCCO  
HATHAWAY P. RUSSELL \*\*  
MARIA LACCOTRIPE ZACHARAKIS, Ph.D.  
PETER A. DIMATTIA  
VINCENT P. LOCCISANO  
MERIDETH C. ARNOLD

SENIOR COUNSEL  
JAMES E. COCKFIELD

OF COUNSEL  
JEREMIAH LYNCH  
WILLIAM A. SCOFIELD, JR.  
SIBLEY P. REPPERT

PATENT AGENTS  
THEODORE R. WEST  
SHAYNE Y. HUFF, Ph.D.  
DANIEL B. KO

TECHNICAL SPECIALISTS  
CYNTHIA M. SOROOS  
PETER W. DINI, Ph.D.  
EUIHOON LEE  
JENNIFER K. ROSENFELD  
ALLAN TAMESHTIT, Ph.D.  
CATHERINE E. McPHERSON  
ERIC F. WAGNER, Ph.D.  
SHAHID HASAN, Ph.D.  
JACOB G. WEINTRAUB  
JONATHAN M. SPARKS, Ph.D.  
CRISTIN E. HOWLEY, Ph.D.

\* Admitted in NY only  
\*\* Admitted in TX only

RECEIVED

DEC 27 2002

TECH CENTER 1600/2900

Commissioner for Patents  
Washington, D.C. 20231

Re: U.S. Patent Application No.: 09/914451  
For: *DRUG DESIGN BASED ON THE STRUCTURE OF LTA<sub>4</sub> HYDROLASE*  
Inventors: Jesper Z. Haeggström *et al.*  
Filed: August 27, 2001  
Our Ref. No.: PVZ-006US

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Information Disclosure Statement;
2. PTO Form 1449;
3. Copies of references cited in PTO Form 1449 (43); and
4. A Return Postcard.

No additional costs are believed to be due in connection with the filing of this Information Disclosure Statement. However, please charge any necessary fees in connection with the enclosed statement to our Deposit Order Account No. 12-0080. For this purpose, a duplicate of this sheet is attached.

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on:

12/17/02  
Date

Elizabeth A. Hanley, Reg. No. 33,505

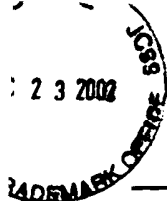
Respectfully submitted,  
LAHIVE & COCKFIELD, LLP

Elizabeth A. Hanley  
Registration No. 33,505  
Attorney for Applicants



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

2 3 2002



In re the application of: Jesper Z. Haeggström *et al.*

Serial No.: 09/914451

Filed: August 27, 2001

For: *DRUG DESIGN BASED ON THE STRUCTURE OF LTA<sub>4</sub> HYDROLASE*

Attorney Docket No.: PVZ-006US

Group Art Unit: 1642

Examiner: Not yet assigned

**RECEIVED**

DEC 27 2002

TECH CENTER 1600/2900

Commissioner for Patents  
Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR §1.8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on the date set forth below.

12/19/02  
Date of Signature and of Mail Deposit

By:

Elizabeth A. Hanley  
Elizabeth A. Hanley  
Registration No. 33,505  
Attorney for Applicants

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicants and their Attorney are aware of the following publications and information, listed on the attached PTO Form 1449, and in accordance with 37 CFR §1.97 hereby submit these publications for the Examiner's consideration. A copy of each cited publication is enclosed.

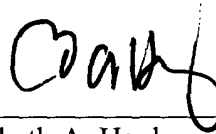
This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other

11. 7/2/54  
12. 7/2/54  
13. 7/2/54  
14. 7/2/54  
15. 7/2/54  
16. 7/2/54  
17. 7/2/54  
18. 7/2/54  
19. 7/2/54  
20. 7/2/54  
21. 7/2/54  
22. 7/2/54  
23. 7/2/54  
24. 7/2/54  
25. 7/2/54  
26. 7/2/54  
27. 7/2/54  
28. 7/2/54  
29. 7/2/54  
30. 7/2/54  
31. 7/2/54  
32. 7/2/54  
33. 7/2/54  
34. 7/2/54  
35. 7/2/54  
36. 7/2/54  
37. 7/2/54  
38. 7/2/54  
39. 7/2/54  
40. 7/2/54  
41. 7/2/54  
42. 7/2/54  
43. 7/2/54  
44. 7/2/54  
45. 7/2/54  
46. 7/2/54  
47. 7/2/54  
48. 7/2/54  
49. 7/2/54  
50. 7/2/54  
51. 7/2/54  
52. 7/2/54  
53. 7/2/54  
54. 7/2/54  
55. 7/2/54  
56. 7/2/54  
57. 7/2/54  
58. 7/2/54  
59. 7/2/54  
60. 7/2/54  
61. 7/2/54  
62. 7/2/54  
63. 7/2/54  
64. 7/2/54  
65. 7/2/54  
66. 7/2/54  
67. 7/2/54  
68. 7/2/54  
69. 7/2/54  
70. 7/2/54  
71. 7/2/54  
72. 7/2/54  
73. 7/2/54  
74. 7/2/54  
75. 7/2/54  
76. 7/2/54  
77. 7/2/54  
78. 7/2/54  
79. 7/2/54  
80. 7/2/54  
81. 7/2/54  
82. 7/2/54  
83. 7/2/54  
84. 7/2/54  
85. 7/2/54  
86. 7/2/54  
87. 7/2/54  
88. 7/2/54  
89. 7/2/54  
90. 7/2/54  
91. 7/2/54  
92. 7/2/54  
93. 7/2/54  
94. 7/2/54  
95. 7/2/54  
96. 7/2/54  
97. 7/2/54  
98. 7/2/54  
99. 7/2/54  
100. 7/2/54

relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

Under 37 C.F.R. § 1.97(b)(3), no additional costs are believed to be due in connection with the filing of this disclosure. If, however, a first Office Action on the merits issues in this application bearing a mailing date prior to the date of this Information Disclosure Statement, please charge the appropriate fee as required under 37 CFR §1.17(p) to our Deposit Order Account No. 12-0080.

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP



Elizabeth A. Hanley  
Registration No. 33,505  
Attorney for Applicants

28 State Street  
Boston, MA 02109  
(617) 227-7400

Date: 12/19/02

EAH/MCA/alf  
Enclosures

1-1-1-1-1

1-1-1-1-1

1-1-1-1-1

1-1-1-1-1

APPLICANT FACSIMILE OF FORM PTO-1449

REV. 10-80

U.S. DEPARTMENT OF  
COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO

SERIAL NO.

PVZ-006US

09/914457

RECEIVED

LIST OF PUBLICATIONS CITED BY APPLICANT  
(Use several sheets if necessary)

APPLICANT

Jesper Z. Haeggström et al.

FILING DATE

August 27, 2001

GROUP

1642

DEC 27 2002

TECH CENTER 1600/2900

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

A1	Andberg, M. et al. "Mutation of tyrosine 383 in leukotriene A <sub>4</sub> hydrolase allows conversion of leukotriene A <sub>4</sub> into 5S,6S-dihydroxy-7,9-trans-11,14-cis-eicosatetraenoic acid. Implications for the epoxide hydrolase mechanism," <i>J. Biol. Chem.</i> 1997 Sep 12;272(37):23057-63	
A2	Barrett, A.J. et al. Eds. "336. Introduction: family M1 of membrane alanyl aminopeptidase," in <i>Handbook of proteolytic enzymes</i> 1998 Oct; pp. 994-996	
A3	Blomster, M. et al. "Evidence for a catalytic role of tyrosine 383 in the peptidase reaction of leukotriene A <sub>4</sub> hydrolase," <i>Eur. J. Biochem.</i> 1995 Aug 1;231(3):528-34	
A4	Byrum, R.S. et al. "Determination of the contribution of cysteinyl leukotrienes and leukotriene B <sub>4</sub> in acute inflammatory responses using 5-lipoxygenase- and leukotriene A <sub>4</sub> hydrolase-deficient mice," <i>J. Immunol.</i> 1999 Dec 15;163(12):6810-9	
A5	Chen, X.-S. et al. "Role of leukotrienes revealed by targeted disruption of the 5-lipoxygenase gene," <i>Nature</i> 1994 Nov;372:179-182	
A6	Cramer, A. et al. "DNA shuffling of a family of genes from diverse species accelerates directed evolution," <i>Nature</i> 1998 Jan 15;391(6664):288-91	
A7	Devchand, P.R. et al. "The PPAR $\alpha$ -leukotriene B <sub>4</sub> pathway to inflammation control," <i>Nature</i> 1996 Nov 7;384(6604):39-43	
A8	Dittmann, K.H. et al. "MK-886, a leukotriene biosynthesis inhibitor, induces antiproliferative effects and apoptosis in HL-60 cells," <i>Leuk. Res.</i> 1998 Jan;22(1):49-53	
A9	Drazen, J.M. et al. "Treatment of asthma with drugs modifying the leukotriene pathway," <i>N. Engl. J. Med.</i> 1999 Jan 21;340(3):197-206	
A10	Evans, J.F. "Leukotriene A <sub>3</sub> . A poor substrate but a potent inhibitor of rat and human neutrophil leukotriene A <sub>4</sub> hydrolase," <i>J. Biol. Chem.</i> 1985 Sep 15;260(20):10966-70	
A11	Ford-Hutchinson, A.W. et al. "Leukotriene B <sub>4</sub> , a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes," <i>Nature</i> 1980 July 17;286:264-65	
A12	Funk, C.D. et al. "Molecular cloning and amino acid sequence of leukotriene A <sub>4</sub> hydrolase," <i>Proc. Natl. Acad. Sci. USA</i> 1987 Oct;84(19):6677-81	
A13	Griffiths, R.J. et al. "Leukotriene B <sub>4</sub> plays a critical role in the progression of collagen-induced arthritis," <i>Proc. Natl. Acad. Sci. USA</i> 1995 Jan 17;92(2):517-21	
A14	Griffiths, R.J. et al. "Collagen-induced arthritis is reduced in 5-lipoxygenase-activating protein-deficient mice," <i>J. Exp. Med.</i> 1997 Mar 17;185(6):1123-9	
Examiner		Date Considered
*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.		

1940-1941  
1942-1943  
1944-1945

1946-1947



APPLICANT FACSIMILE OF FORM PTO-1449

U.S. DEPARTMENT OF  
COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO

SERIAL NO.

RECEIVED

PVZ-006US

09/91445

LIST OF PUBLICATIONS CITED BY APPLICANT  
(Use several sheets if necessary)

APPLICANT

Jesper Z. Haeggström et al.

DEC 27 2002

FILING DATE

August 27, 2001

GROUP

1642

TECH CENTER 1600/2900

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

B1	Haeggström, J.Z. et al. "Leukotriene A <sub>4</sub> hydrolase: structural and functional properties of the active center," <i>J. Lipid Mediat.</i> 1993 Mar-Apr;6(1-3):1-13
B2	Hogg, J.H. et al. "Probing the activities and mechanisms of leukotriene A <sub>4</sub> hydrolase with synthetic inhibitors," <i>Chem. Eur. J.</i> 1998;4(9):1698-1713
B3	Kuchner, O. et al. "Directed evolution of enzyme catalysts," <i>Trends Biotechnol.</i> 1997 Dec;15(12):523-30
B4	Labaudinière, R. et al. "ω-[(ω-Arylkyl)thienyl]alkanoic acids: from specific LTA <sub>4</sub> hydrolase inhibitors to LTB <sub>4</sub> receptor antagonists," <i>J. Med. Chem.</i> 1992 Aug 21;35(17):3170-9
B5	Lewis, R.A. et al. "Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases," <i>N. Engl. J. Med.</i> 1990 Sep 6;323(10):645-55
B6	Lorsch, J.R. et al. "In vitro evolution of new ribozymes with polynucleotide kinase activity," <i>Nature</i> 1994 Sep 1;371(6492):31-6
B7	Medina, J.F. et al. "Leukotriene A <sub>4</sub> hydrolase: determination of the three zinc-binding ligands by site-directed mutagenesis and zinc analysis," <i>Proc. Natl. Acad. Sci. USA</i> 1991 Sep 1;88(17):7620-4
B8	Ménard, A. et al. "The cytotoxic activity of Bacillus anthracis lethal factor is inhibited by leukotriene A <sub>4</sub> hydrolase and metalloproteinase inhibitors," <i>Biochem. J.</i> 1996 Dec 1;320 ( Pt 2):687-91
B9	Mueller, M.J. et al. "Leukotriene A <sub>4</sub> hydrolase: mapping of a hencosapeptide involved in mechanism-based inactivation," <i>Proc. Natl. Acad. Sci. USA</i> 1995 Aug 29;92(18):8383-7
B10	Mueller, M.J. et al. "Leukotriene A <sub>4</sub> hydrolase: protection from mechanism-based inactivation by mutation of tyrosine-378," <i>Proc. Natl. Acad. Sci. USA</i> 1996 Jun 11;93(12):5931-5
B11	Mueller, M.J. et al. "Leukotriene A <sub>4</sub> hydrolase, mutation of tyrosine 378 allows conversion of leukotriene A <sub>4</sub> into an isomer of leukotriene B <sub>4</sub> ," <i>J. Biol. Chem.</i> 1996 Oct 4;271(40):24345-8
B12	Nord, K. et al. "Binding proteins selected from combinatorial libraries of an alpha-helical bacterial receptor domain," <i>Nat. Biotechnol.</i> 1997 Aug;15(8):772-7
B13	Orning, L. et al. "Inhibition of leukotriene A <sub>4</sub> hydrolase/aminopeptidase by captopril," <i>J. Biol. Chem.</i> 1991 Sep 5;266(25):16507-11
B14	Orning, L. et al. "The bifunctional enzyme leukotriene- A <sub>4</sub> hydrolase is an arginine aminopeptidase of high efficiency and specificity," <i>J. Biol. Chem.</i> 1994 Apr 15;269(15):11269-73

Examiner

Date Considered

\*EXAMINER:

Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[illegible]

DEC 23 2002  
TRADEMARK OFFICE

APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO <b>PVZ-006US</b>	SERIAL NO. <b>09/914451</b>
LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT <b>Jesper Z. Ha ggstr"m et al.</b>	
		FILING DATE <b>August 27, 2001</b>	GROUP <b>1642</b>

RECEIVED

DEC 27 2002

U.S. PATENT DOCUMENTS

TECH CENTER 1600/2900

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

C1	Owman, C. et al. "The leukotriene B <sub>4</sub> receptor functions as a novel type of coreceptor mediating entry of primary HIV-1 isolates into CD4-positive cells," <i>PNAS. USA</i> 1998 Aug 4;95(16):9530-4	
C2	Rola-Pleszczynski, M. et al. "Leukotrienes augment interleukin 1 production by human monocytes," <i>J. Immunol.</i> 1985 Dec;135(6):3958-61	
C3	Samuelsson, B. "Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation," <i>Science</i> 1983 May 6;220(4597):568-75	
C4	Samuelsson, B. et al. "Leukotrienes and lipoxins: structures, biosynthesis, and biological effects," <i>Science</i> 1987 Sep 4;237(4819):1171-6	
C5	Serhan, C.H. et al. "Lipid mediator networks in cell signaling: update and impact of cytokines," <i>FASEB J.</i> 1996 Aug;10:1-12	
C6	Tsuge, H. et al. "Crystallization and preliminary X-ray crystallographic studies of recombinant human leukotriene A <sub>4</sub> hydrolase complexed with bestatin," <i>J. Mol. Biol.</i> 1994 May 20;238(5):854-6	
C7	Vallee, B.L. et al. "Active-site zinc ligands and activated H <sub>2</sub> O of zinc enzymes," <i>Proc. Natl. Acad. Sci. USA</i> 1990 Jan;87(1):220-4	
C8	Wetterholm, A. et al. "Recombinant mouse leukotriene A <sub>4</sub> hydrolase: a zinc metalloenzyme with dual enzymatic activities," <i>Biochim. Biophys. Acta</i> 1991 Oct 25;1080(2):96-102	
C9	Wetterholm, A. et al. "Leukotriene A <sub>4</sub> hydrolase: abrogation of the peptidase activity by mutation of glutamic acid-296," <i>Proc. Natl. Acad. Sci. USA</i> 1992 Oct 1;89(19):9141-5	
C10	Wetterholm, A. et al. "Potent and selective inhibitors of leukotriene A <sub>4</sub> hydrolase: effects on purified enzyme and human polymorphonuclear leukocytes," <i>J. Pharmacol. Exp. Ther.</i> 1995 Oct;275(1):31-7	
C11	Yamaoka, K.A. et al. "Leukotriene B <sub>4</sub> enhances activation, proliferation, and differentiation of human B lymphocytes," <i>J. Immunol.</i> 1989 Sep 15;143(6):1996-2000	
C12	Yokomizo, T. et al. "A G-protein-coupled receptor for leukotriene B <sub>4</sub> that mediates chemotaxis," <i>Nature</i> 1997 Jun 5;387(6633):620-4	
C13	Yokomizo, T. et al. "A second leukotriene B <sub>4</sub> receptor, BLT2. A new therapeutic target in inflammation and immunological disorders," <i>J. Exp. Med.</i> 2000 Aug 7;192(3):421-32	
C14	Yuan, W. et al. "Novel tight-binding inhibitors of leukotriene A <sub>4</sub> hydrolase," <i>J. Am. Chem. Soc.</i> 1992 April;114:6552-53	
C15	GenPept Acc. No. S65947; leukotriene-A4 hydrolase (EC 3.3.2.6) long isoform - human	
Examiner		Date Considered
*EXAMINER:		Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

100-100000  
100-100000  
100-100000